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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	**PAPER NUMBER**
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/780,905	PARIS ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,21-24,27,28,30-38 and 61-73* is/are pending in the application.

4a) Of the above claim(s) *32-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15, 21-24, 27-28, 30-31 and 61-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the reply received on 23 July 2008.

Any rejection from the previous office action, which is not restated here, is withdrawn.

Status of the claims

Claims 15, 21-24, 27-28, 30-38, 62-73 are pending in the application. Claims 15, 62, 64-71 were amended by applicant. Claims 72-73 are new.

Applicant originally elected L-685,458 which was searched and found free of the prior art (however, please see 112 1st rejection below). The search was expanded and the species DAPT was found.

Claims 15, 21-24, 27-28, 30-31, 62-73 are presented for examination on the merits. Claims 32-38 are withdrawn as not drawn to the elected species.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15, 21-24, 27-28, 30-31, 62-73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 15, 21-24, 26-28, 30-38, 61-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s)

contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic (such as "secretase inhibitor"), without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a method of reducing solid tumor volume in an animal or human in need thereof, comprising administering to said animal or human a therapeutically effective amount in unit dosage form of a composition comprising at least one secretase inhibitor that inhibits gamma-secretase or beta-secretase processing of amyloid precursor protein (APP), said amount being effective to inhibit angiogenesis and to reduce solid tumor volume in said animal or human. In regards to the "secretase inhibitor" term, this is a very broad generic statement drawn to any secretase inhibitor, there exists a plethora of such compounds, which are not adequately described and/or represented in the examples. The claims are drawn to methods of reducing solid tumor volume with at least one secretase inhibitor that inhibits gamma-secretase or beta -secretase processing of APP (amended claim 15). Dependent claims contain claims drawn to specific core structures, however, the secretase inhibitors of claim 15 are only functionally described. The disclosure provides the following examples: Example 1 ([0065]-[0076] of the corresponding publication of the present application) is drawn to the effects of aspartyl protease transition-state gamma-secretase inhibitor L-685,458; the dipeptide protease gamma-secretase inhibitors DAPM and DAPT, the isocoumarin-based serine protease gamma-secretase inhibitro JLK-6, ; the substrate analogue peptide .beta.-secretase inhibitors Z-VLL-CHO and GLI89; and the peptidomimetic tight binding transition-state analogue .beta.-secretase inhibitor OM99-2, on the proliferation and differentiation of primary cultures of human brain endothelial cells, on capillary morphogenesis, and on the processing of APP in human brain endothelial cells, in order to determine the potential role of the APP processing pathway in angiogenesis. Example 2 ([0077]-[0080]) is drawn to the effects of the aspartyl protease transition-state .gamma.-secretase inhibitor L-685,458; the dipeptide protease .gamma.-secretase

inhibitors DAPM and DAPT; the isocoumarin-based serine protease .gamma.-secretase inhibitor JLK-6; the substrate analogue peptide .beta.-secretase inhibitors Z-VLL-CHO, GL189 and P10-P4'statV; and the peptidomimetic tight binding transition-state analogue .beta.-secretase inhibitor OM99-2, on the rat aorta model of angiogenesis, which is known to correlate well with in vivo events of neovascularization. Example 3 ([0081]-[0084]) is drawn to the effects of the dipeptide protease .gamma.-secretase inhibitor DAPT and the substrate analogue peptide .beta.-secretase inhibitor Z-VLL-CHO, on the growth of human glioblastoma U-87 MG tumor cells, xenografted under the skin of nude mice. The Examples are limited to a few species of unrelated secretases, with no structural common core(s) therefore the specification does not sufficiently sufficient examples describing the full breadth of secretase inhibitors instantly claimed, nor does it provide a core structure for such secretase inhibitors (except in dependent claims). As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claim 15 is a broad generic with respect all possible methods encompassed by the claims. It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73

(Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Response to arguments

Applicant's arguments have been carefully considered by Examiner and deemed persuasive with respect to the term solid tumor, however, they are not persuasive with respect to the term “secretase inhibitor” for the reasons of record and for the following reasons: Examiner previously stated that : “With respect to the term “secretase inhibitor”, as set forth above, the disclosure teaches specific examples which can reasonably encompass a subgenus of protease inhibitors which inhibit APP processing and is further drawn to specific core structures” (see Office Action dated 23 January 2008, page 7, lines 5-8). Therefore, amending the broad claim 15 to merely recite a functional limitation is not sufficient to overcome the written description rejection which is precisely based on the purely functional description and lacking a structural core, as previously set forth by Examiner.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15, 21-24, 27-28, 30-31 and 62-71 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weng et al. (Mol. Cell. Biol., January 2003) and over Jundt et al. (Blood, November 16, 2002)

Weng et al. beneficially teach a method of treating a tumor by inhibiting angiogenesis comprising administering to the animal or human a therapeutically effective amount of a secretase inhibitor effective to inhibit angiogenesis and to reduce tumor volume. (See, e.g., abstract, page 656, column 2, lines 28-38, 57-75, page 657, column 1, lines 2-6, 23-35, page 662, column 2, lines 13-16, page 663, column 1, lines 1-59, column 2, lines 1-17, Figs. 2-8).

Weng et al. do not expressly teach an in vivo method of treating a tumor in an animal or human in need thereof and using a carrier in addition to the secretase inhibitor and/or expressly selecting DAPT from amongst the secretase inhibitors listed therein.

Jundt et al. teach a method of treating a tumor (Hodgkin and Anaplastic Large Cell Lymphoma) comprising administering to the animal or human a therapeutically effective amount of a composition comprising a carrier and at least one secretase inhibitor (DAPT). Jundt et al. also teach that gamma-secretases in general, including DAPT might be a novel therapeutic principle to control the proliferation capacity of neoplasms (See entire abstract, Blood 2002, Vol. 100, No. 11, page 158a). DAPT blocked the increase in growth rates of tumor cells of Hodgkin and anaplastic large cell lymphoma activated by their cognate ligand Jagged1.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Weng et al. by expressly using DAPT as taught by Jundt et al. The skilled artisan would have been motivated to do so because both Jundt et al. and Weng et al. teach that DAPT may be used in other types of cancers and neoplasms. There would have been a reasonable expectation of success, given that DAPT had shown tumor cell growth inhibition in vitro as taught by Jundt et al. (last paragraph). The adjustment of particular conventional working conditions (e.g., determining type of neoplasm to be treated, dosage units, carrier, mode of administration and patients within this therapeutic method) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan. As such, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g., type of neoplasm to be treated, dosage units, carrier, mode of administration and patients), because such conditions are art-recognized result-effective variables that are routinely determined and

optimized in the art through routine experimentation ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.". *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2145.05). One would have been motivated to determine all optimum and operable conditions in order to achieve the safest and most effective method in the most efficient manner. One would have had a reasonable expectation for success because such modifications are routinely determined and optimized in the art through routine experimentation.

From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments

Weng discloses the use of recombinant T-cell lines transformed to express Notch-constructs in a study of Notch signaling in regulation of cell growth and differentiation. In particular, Weng reports that presenilin inhibitors alter processing of the Notch constructs and that one specific such inhibitor, DPF-AA, was able to inhibit the growth of one of the recombinantly created cell lines. However, as figure 3 demonstrates (see Weng at page 658), treatment with the presenilin inhibitor merely suppressed the growth rate of target cells. Treated cells initially proliferated at the same rate as controls, which rate eventually slowed such that the cultures exhibited a plateau

phase, characterized by a constant concentration of viable cells. The constant concentration of viable cells suggest that the cultures have stopped proliferating but remain viable, or that the presenilin inhibitor is in fact cytotoxic, but achieving a death rate that is only sufficient to balance the proliferative capacity of the cells, which remains unaffected. Thus, Applicants submit that one of ordinary skill in the art would interpret the teachings of Weng as merely suggestive of a means of slowing cancer cell proliferation or, at most, a means of preventing further growth of the existing tumor burden at treatment start. Thus, Weng cannot suggest a means of reducing solid tumor as instantly claimed in claim 15.

Jundt is directed to a characterization of Jagged1-Notch signaling in Notch-positive Hodgkin and large cell anaplastic lymphoma cell lines. In the sole inhibition study presented, Jundt reports that, in vitro, exposure of these cells lines to Jagged1 results in exponential increase in the cells' respective growth rates, which effect is blocked by the gamma-secretase inhibitor, DAPT. Notably, however, Jundt reports that only that the increase in growth rate caused by Jagged1 exposure is blocked by DAPT, suggesting that DAPT does not affect the original proliferative capacity of the cells. Thus Applicants submit that none of Weng or Jundt is suggestive of a method to reduce solid tumor volume as instanlty claimed in claim 15 and in claims 21-24, 27-28, 30-38 and 62-73 as dependent thereon.

Response to arguments

Applicant's arguments have been carefully considered, but not deemed persuasive for the reasons of record and because Weng teaches use of DAPT (N-N-

3,5-difluorophenacetyl)-L-alanyl-S-phenylglycine (e.g., page 656, column 2, last paragraph) –and other presenilin inhibitor-- in chemotherapeutic studies in general and in specific to slow down or reduce cell proliferation (e.g., Figure 3). Jundt et al. teach a method of treating a tumor (Hodgkin and Anaplastic Large Cell Lymphoma) comprising administering to the animal or human a therapeutically effective amount of a composition comprising a carrier and at least one secretase inhibitor (DAPT). Jundt et al. also teach that gamma-secretases in general, including DAPT might be a novel therapeutic principle to control the proliferation capacity of neoplasms (See entire abstract, Blood 2002, Vol. 100, No. 11, page 158a). DAPT blocked the increase in growth rates of tumor cells of Hodgkin and anaplastic large cell lymphoma activated by their cognate ligand Jagged1. It would have been obvious to one of ordinary skill in the art to utilize DAPT, a secretase inhibitor encompassed by the instant claims in solid tumors (neoplams) as taught by Jundt et al., which necessarily reads upon the instantly claimed method steps and would therefore "reduce volume" of the neoplasm, as stated by Jundt that DAPT potently inhibits tumor cell growth in vivo and that it might be a novel therapeutic principle to control the proliferation capacity of neoplasms. Therefore, the 103 obviousness rejection is maintained.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654

/Marcela M Cordero Garcia/
Examiner, Art Unit 1654

MMCG 11/08